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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SMITH, CAROLYN L	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 12/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/885,827	SALVATI ET AL.	
	Examiner	Art Unit	
	Carolyn L Smith	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments and remarks, filed 9/27/04, are acknowledged. Amended claim 1 and new claim 25 are acknowledged.

Applicant's arguments, filed 9/27/04, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from the previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 1-7 and 25 are herein under examination.

Claims Rejected Under 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology

is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

LACK OF SCOPE OF ENABLEMENT

The rejection of claims 1-7 is maintained under 35 U.S.C. 112, first paragraph and newly applied to new claim 25, because the specification, while being enabling for the atomic structural coordinate listing (Table A) of an androgen receptor-ligand binding domain (AR-LBD), does not reasonably provide enablement for a method of inhibiting the growth of hormone-dependent tumor cells by administering a selective androgen receptor modulator that exhibits antagonist activity in a hormone-dependent tumor while exhibiting no activity or agonist activity against other non-tumor tissues containing the androgen receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

This rejection is maintained (for claims 1-7) and necessitated by amendment for new claim 25.

Applicants state that claims 1-7 and 9 are rejected. This statement is incorrect as claim 9 was not under examination. Currently claims 1-7 and 25 are rejected due to a lack of scope of enablement. Applicants point out the specification on page 45, lines 5-7, states "all of the exemplary compounds in the above Table [Table 1] demonstrated a SARM profile in accordance with the present invention." This statement is acknowledged. It is noted that the compounds in Table 1 appear to be SARMs for an androgen receptor (AR) with a ligand binding domain (LBD) containing the structural coordinates as listed in Table A of the specification. The SARMs in

Table 1 are therefore representative examples of SARMs for an androgen receptor with those particular coordinates. However, in the *Journal of Biological Chemistry* (2000, Vol. 275, No. 34, pages 26164-26171), Matias et al. state that mutations in the AR LBD gene can create mutations within regions involved in ligand binding (page 26169, second paragraph in col. 1 to first paragraph in col. 2). In the same reading passage, Matias et al. state for most of the mutations, a structural effect can be associated with the substitution. One of skill in the art would not conclude that the SARMs listed in Table 1 of the instant application would be effective for all AR LBDs found in nature due to variations in binding site structures. Other AR including their LBDs would need to be crystallized to determine if SARMs would bind and exhibit effects on these other ARs. However, a method that relies on data from an unpredictable art such as protein crystallization would require clear and precise guidance for one skilled in the art to reliably use the said methods. As the science of protein crystallization is well known to be a trial and error procedure with unpredictable results (Drenth, page 1, lines 13-20), one skilled in the art would require clear and precise guidance to make any particular crystal in order to obtain structural coordinates for a three-dimensional model. Accordingly, it would be very difficult for a skilled artisan to make crystal structures of other androgen receptor complexes beyond that mentioned in the instant case where specific coordinates are disclosed. Due to the unpredictability and difficulty of crystallizing proteins, it is unlikely that one of skill in the art would be able to make another crystal relying solely on the information for the crystal disclosed in the specification without undue experimentation. Again, due to the unpredictability in the art, a skilled artisan could not reasonably expect to make and use the structural coordinates from any

androgen receptor complex based on generic guidelines of making crystals without undue experimentation.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. (e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 1-7 is maintained and newly applied to claim 25 under 35 U.S.C. 103(a) as being unpatentable over Thorpe et al. (P/N 6,004,554), in view of Zhi et al. (P/N 6,358,947) and Li et al. (P/N 6,469,024).

This rejection is necessitated by amendment.

Thorpe et al. describe treating tumors by using immunological reagents to target tumor-associated vascular endothelial cells in combination with direct targeting of tumor cells (col. 3, lines 45-52 and Table II on col. 25-26). Thorpe et al. describe therapeutic agents that have cytotoxic or anticellular effect by suppressing growth or division of cells (col. 3, lines 57-64). Thorpe et al. describe these methods and compositions as applicable to solid tumors, including carcinomas of the prostate (col. 4, lines 1-11 and Fig. 15A). Thorpe et al. describe a therapeutic method employing an antibody having high selectivity for tumor cells and little or no reactivity with the cell surface of normal endothelial cells (col. 5, lines 30-36). Thorpe et al. describe therapeutics showing no significant reactivity with normal tissues, including kidney, brain, liver, bone marrow, prostate, thyroid, muscle, skin, or other normal organ or tissue in the human body (col. 25-26, lines 64-67) which represents maintaining average bone density and muscle mass as seen in ugonadal warm-blooded male mammals. Thorpe et al. describe therapeutic doses did not cause detectable damage and all bone marrow cell populations were normal 20 days after treatment (col. 46, lines 16-23). Thorpe et al. describe and therefore suggest attaching other agents to target the toxin moiety to a tumor, such as hormones (col. 30, lines 34-43). Thorpe et al. do not specifically mention selective androgen receptor modulators.

Zhi et al. describe compounds that modulate a process mediated by androgen receptors (col. 19, lines 20-23), including male hormone response diseases (col. 19, lines 26-27). Zhi et al. describe a method of treating prostate adenocarcinomas, carcinomas, benign prostatic hypertrophy of prostate, and other hormone-dependent tumors by administering a pharmaceutically effective amount of a compound (col. 20, lines 9-25).

Li et al. describe methods for treating osteoporosis by administering a therapeutically effect amount of a compound which stimulates an increase in muscle mass (col. 5, lines 13-21 and col. 208, lines 50-52) which represents exhibiting an agonist activity against non-tumor tissues. Li et al. describe a method for increasing growth hormone levels by administering a compound (col. 5, lines 7-12). Li et al. describe using the compounds in combination with a selective androgen receptor modulator to treat, stimulate, and increase muscle mass, as well as reducing cachexia due to cancer (col. 44, lines 47-61). Li et al. describe using the compounds in combination with anti-tumor agents (col. 49, lines 1-4). Li et al. describe treating Alzheimer's disease (col. 45, line 51), anorexia (col. 45, lines 38-39), and muscular atrophy due to physical inactivity and bed rest (col. 46, lines 24-26) by administering a therapeutically effective amount of a compound (col. 45, lines 3-8; col. 208, lines 32-35; and col. 209, lines 7-9).

Thorpe et al. state that significant advances in chemotherapy have been made for some tumors, while other types of tumors resist chemotherapeutic intervention (col. 1, lines 39-41). Thorpe et al. point out the key to developing successful antitumor agents is to design them to selectively kill tumor cells while exerting little effect against normal tissues (col. 1, lines 65-67 and col. 2, line 1). Thorpe et al. state this has been difficult because of the few qualitative differences between neoplastic and normal tissues (col. 2, lines 1-3). Thorpe et al. state much research has focused on identifying tumor-specific "marker antigens" (col. 2, lines 3-6). As Thorpe et al. state, modifications can be made without departing from the spirit and scope of their invention (col. 31, lines 48-53), a skilled artisan in the art would have reasonable expectation of success to enhance the methods for inhibiting and treating prostate tumors, as stated by Thorpe et al., by administering various compounds related to prostate, as stated by Zhi

et al. and Li et al. Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to include the administration of selective androgen receptor modulators (as stated by Zhi et al. and Li et al.) in the methods of inhibiting and treating prostate tumor cells (as stated by Thorpe et al.) with a reasonable expectation of success. The motivation to do so is given by Thorpe et al. who teach developing successful antitumor agents via selective target agents (col. 1, lines 65-67), and the teaching of Zhi et al. and Li et al. relating to compounds that target androgen receptors.

Thus, Thorpe et al., in view of Zhi et al. and Li et al. motivate the instant invention.

Applicants state claims 1-7 and 9 are rejected under 35 USC 103(a). This statement is incorrect as claim 9 was not under examination. Currently, claims 1-7 and 25 are rejected under 35 USC 103 (a). Applicants state the SARM itself must have the two features of exhibiting antagonist activity inhibiting growth of said hormone-dependent tumor as well as exhibiting no or agonist activity against other, nontumor tissues containing the androgen receptor. This statement is found unpersuasive as the instant claims and specification do not mention that the SARM refers the SARM itself with no other compound. The SARM has been broadly and reasonably interpreted to include other compounds that may be present in the administration mixture. Thus, Applicants statements are found unpersuasive.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR §1.6(d)). The CM1 Fax Center number is (703) 872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carolyn Smith, whose telephone number is (571) 272-0721. The examiner can normally be reached Monday through Thursday from 8 A.M. to 6:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (571) 272-0722.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner Tina Plunkett whose telephone number is (571) 272-0549.

Ardin H. Marschel 12/6/04
ARDIN H. MARSCHEL
PRIMARY EXAMINER

December 6, 2004